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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CELGENE CORPORATION, **Plaintiff,** **v.** **HETERO LABS LIMITED, HETERO LABS LIMITED UNIT-V, HETERO DRUGS LIMITED, HETERO USA, INC., AUROBINDO PHARMA LIMITED, AUROBINDO PHARMA USA, INC., AUROLIFE PHARMA LLC, EUGIA PHARMA SPECIALTIES LIMITED, APOTEX INC., APOTEX CORP., MYLAN PHARMACEUTICALS, INC., MYLAN INC., MYLAN, N.V., and BRECKENRIDGE PHARMACEUTICAL, INC.,** **Defendants.**	**Civil Action No. 17-3387 (ES)(JAD)** **(Filed Electronically)**

CELGENE CORPORATION'S REPLY TO HETERO LABS LIMITED, HETERO LABS LIMITED UNIT-V, HETERO DRUGS LIMITED, AND HETERO USA, INC.'S COUNTERCLAIMS AND COUNTER-COUNTERCLAIMS TO HETERO LABS LIMITED, HETERO LABS LIMITED UNIT-V, HETERO DRUGS LIMITED, AND HETERO USA, INC.'S COUNTERCLAIMS

Celgene Corporation ("Celgene"), by its undersigned attorneys, replies to the Counterclaims to Plaintiff's Complaint for Patent Infringement by Hetero Labs Limited, Hetero

Labs Limited Unit-V, Hetero Drugs Limited, and Hetero USA, Inc.'s (together, "Hetero") dated July 13, 2017 as follows. Except as expressly admitted, all allegations are denied.

1. Hetero repeats and incorporates by reference each of the foregoing paragraphs of Hetero's Answer and Affirmative Defenses to the Complaint.

REPLY: This paragraph does not require a reply because it does not allege counterclaims. Celgene denies Hetero's separate defenses and repeats and incorporates by reference the allegations in Celgene's Complaint (D.I. 1) as if set forth fully herein.

The Parties

2. Hetero Labs Limited is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad – 500 018, Andhra Pradesh, India.

REPLY: Celgene admits on information and belief the allegations of paragraph 2.

3. Hetero Labs Limited Unit-V is a division of Hetero Labs Limited and is located at Polepally, Jadcherla, Mahabubnagar – 509 301, Andhra Pradesh, India.

REPLY: Celgene admits on information and belief the allegations of paragraph 3.

4. Hetero USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854.

REPLY: Celgene admits on information and belief the allegations of paragraph 4.

5. Upon information and belief, Plaintiff/Counter-Defendant Celgene is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

REPLY: Celgene admits that Celgene Corporation is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901, and except as so admitted, denies the allegations of paragraph 5.

Jurisdiction

6. These Counterclaims arise under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("MMA") (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

REPLY: Paragraph 6 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene denies the legal sufficiency of Hetero's Counterclaims, denies that Hetero is entitled to the declarations it seeks, and denies the remaining allegations of paragraph 6.

7. This Court has original jurisdiction over the subject matter of these Counterclaims under 28 U.S.C. §§ 1331 and 1338(a); under the Declaratory Judgment Act, and 28 U.S.C. §§ 2201 and 2202, and under the MMA (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

REPLY: Paragraph 7 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene denies the legal sufficiency of Hetero's Counterclaims and denies that Hetero is entitled to the declarations it seeks, admits that this Court has subject matter jurisdiction over these Counterclaims, and, except as so admitted, denies the allegations of paragraph 7.

8. This court has subject matter jurisdiction over these Counterclaims for declaratory judgment pursuant to 28 U.S.C. §§ 1331, 1337(a), 1338(a), 2201(a) and (b), and 2202, based on an actual controversy between Hetero and Plaintiff/Counterclaim-Defendant, arising under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

REPLY: Paragraph 8 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits that this Court has subject matter jurisdiction and declaratory judgment jurisdiction over Hetero's Counterclaims as to the patents-in-suit for purposes of this specific action only, admits that there is an actual and justiciable controversy between the parties, and denies that Hetero is entitled to any of the relief that it seeks, and, except as so admitted, denies the allegations of paragraph 8.

9. This court has personal jurisdiction over Plaintiff/Counterclaim-Defendant based, *inter alia,* on the filing of this lawsuit in this jurisdiction and because Plaintiff/Counterclaim-Defendant is doing business in this jurisdiction.

REPLY: Paragraph 9 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits that, for purposes of this specific action only, this Court has personal jurisdiction over it, and, except as so admitted, denies the allegations of paragraph 9.

10. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c), and 1400(b).

REPLY: Paragraph 10 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits that venue is proper to adjudicate this action and, except as so admitted, Celgene denies the allegations of paragraph 10.

Background

I. FDA Approval of Brand Name Drugs – New Drug Applications ("NDA's")

11. The Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 et seq., as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (commonly known as the "Hatch-Waxman Amendments" or "Hatch-Waxman Act" or "Hatch-Waxman "), and as further amended by the MMA, sets forth the rules that the U.S. Food and Drug Administration ("FDA") follows when considering whether to approve both brand-name and generic drugs.

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq*. contains statutory provisions relating to food and drugs, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 11.

12. Under the FFDCA, as amended by Hatch-Waxman and the MMA, an applicant seeking to market a brand-name drug that has not been previously approved must prepare a New Drug Application ("NDA") for consideration by the FDA. *See* 21 U.S.C. § 355.

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq*. contains statutory provisions relating to food and drugs, including applications to market new drugs, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 12.

13. An NDA must include, among other things, the number of any patent that claims the "drug" or a "method of using [the] drug" for which the NDA was submitted and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. *See* 21 U.S.C. §§ 355(b)(1), (c)(2); 21 C.F.R. §§ 314.53(b), (c)(2).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq*. contains statutory provisions relating to food and drugs, that 21 C.F.R. contains regulations relating to food and drugs, including provisions concerning identification of patents covering approved drugs, refers to the statutes and regulations for the terms thereof and, except as so admitted, denies the allegations of paragraph 13.

14. Upon approval of the NDA, the FDA publishes patent information for the approved drug in its publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." *See* 21 U.S.C. § 355(j)(7)(A)(iii).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq*. contains statutory provisions relating to food and drugs, including publication by the United States Food and Drug Administration ("FDA") of the "Approved Drug Products with Therapeutic Equivalence Evaluations" commonly called the "Orange Book," refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 14.

II. Generic Competition – Abbreviated New Drug Applications ("ANDAs")

15. In 1984, Congress enacted the Hatch-Waxman Amendments to the FFDCA. Congress passed Hatch-Waxman, which simplified the procedure for obtaining approval of generic drugs with the purpose of decreasing the price of pharmaceuticals through increased competition. Under Hatch-Waxman, a generic manufacturer submits what is called an Abbreviated New Drug Application ("ANDA").

REPLY: Celgene admits that Congress passed the Drug Price Competition and Patent Term Restoration Act, sometimes referred to as the "Hatch-Waxman Act," refers to the statutes for the terms thereof, admits that the Hatch-Waxman Act governs the filing of ANDAs, and except as so admitted, denies the allegations of paragraph 15.

16. To receive approval of its ANDA, an applicant must, inter alia, show that its generic drug is "bioequivalent" to the Reference Listed Drug, the Orange Book listed drug identified as the drug product upon which the ANDA applicant relies upon in seeking approval of its ANDA. *See* 21 U.S.C. § 355(j)(4)(F); 21 C.F.R. 314.3(b).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, that 21 C.F.R. contains regulations relating to food and drugs, including provisions concerning bioequivalence, refers to the statutes and regulations for the terms thereof and, except as so admitted, denies the allegations of paragraph 16.

17. When filing an ANDA seeking approval of a generic version of a drug listed in the Orange Book, the ANDA applicant must also "certify" that any patent information listed in the Orange Book does not preclude FDA approval of a generic version of the drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, that 21 C.F.R. contains regulations relating to food and drugs, including provisions concerning patent certifications, refers to the statutes and regulations for the terms thereof and, except as so admitted, denies the allegations of paragraph 17.

18. With certain exceptions not applicable here, when seeking FDA approval to market prior to patent expiration, an ANDA applicant can submit a so-called "Paragraph IV certification" asserting that, in the applicant's opinion and to the best of its knowledge, the listed patent is invalid, unenforceable, and/or will not be infringed. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 18.

19. An applicant submitting an ANDA containing a paragraph IV certification must notify both the patent holder and NDA-holder of its paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(B).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 19.

20. If the patent owner brings suit within 45 days of receiving the notice required by 21 U.S.C. § 355(j)(2)(B), the FDA cannot approve the ANDA for 30 months, unless the district court enters an order shortening that period. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Thus, patent owners have a significant financial incentive to file suit regardless of merit (or lack thereof).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 20.

21. If the court hearing the infringement action rules before the expiration of the 30-month period that the patent is invalid, unenforceable, or not infringed, the FDA may approve the ANDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq*. contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 21.

22. If the patent owner does not file such a suit, the ANDA applicant can file and maintain a suit for declaratory judgment against the NDA-holder/patent owner to obtain patent certainty. Indeed, Congress explicitly mandated in the MMA amendments to the FFDCA and Hatch-Waxman that an ANDA applicant is entitled to bring and maintain a declaratory judgment action when it is not sued. *See* 21 U.S.C. § 355(j)(5)(C); 35 U.S.C. § 271(e)(5).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 22.

23. Under the MMA, an ANDA applicant who has filed a paragraph IV certification is statutorily entitled to institute and maintain an action for declaratory judgment against an NDA-holder/patent owner if: (1) the 45-day period has passed since notice of the paragraph IV certification was received; (2) neither the patent owner nor the NDA-holder brought an action for infringement of the patent within the 45-day period; and, (3) the notice of paragraph IV certification contains an Offer of Confidential Access to the ANDA if the applicant asserts non-infringement. *See* 21 U.S.C. §§ 355(j)(5)(C)(i)(I)(aa)-(cc).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 23.

24. Once these three conditions are met, the MMA specifically and unequivocally provides that an ANDA applicant "may, in accordance with section 2201 of title 28 [of the United States Code] bring a civil action under such section against the owner or holder referred to in such subclause . . . for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval . . . ." 21 U.S.C. § 355(j)(5)(C)(i)(II); *see also* 35 U.S.C. § 271(e)(5).

REPLY: Celgene admits that 21 U.S.C. § 301 *et seq.* contains statutory provisions relating to food and drugs, including provisions concerning patent certifications, refers to the statutes for the terms thereof and, except as so admitted, denies the allegations of paragraph 24.

25. An ANDA applicant may exercise its right to file and maintain a declaratory judgment action under the MMA regardless of whether or not the Offer of Confidential Access to the Application is accepted.

REPLY: Paragraph 25 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene denies the allegations of paragraph 25.

26. The declaratory judgment provision contained in the MMA, Section 1101 of the MMA, 117 Stat. 2066, 2454-2456, applies to all ANDAs pending on or after December 8, 2003, which includes the ANDA at issue in these proceedings.

REPLY: Paragraph 26 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene denies the allegations of paragraph 26.

Facts Common to All Counts

27. This is an action for a declaratory judgment of non-infringement and invalidity of one or more claims of U.S. Patent Nos.: 8,198,262 ("the '262 patent), 8,673,939 ("the '939 patent"), 8,735,428 ("the '428 patent"), 8,828,427 ("the '427 patent"), 6,315,720 ("the '720 patent"), 6,561,977 ("the '977 patent"), 6,755,784 ("the '784 patent"), 8,315,886 ("the '886 patent"), and 8,626,531 ("the '531 patent"), (collectively, "the Patents-in-Suit.)

REPLY: Paragraph 27 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that the Counterclaims purport to seek a declaration that one or more claims of the patents-in-suit are invalid and/or will not be infringed, but Celgene denies the legal sufficiency of Hetero's Counterclaims and denies that Hetero is entitled to the declarations it seeks, and except as so admitted, denies the allegations of paragraph 27.

28. Upon information and belief, true and correct copies of the '262, '939, '428, and '427 patents are attached to Plaintiff/Counter-Defendant's Complaint as Exhibits A-D, respectively. Upon information and belief, true and correct copies of the '720, '977, '784, '886, and '531 patents are attached hereto as Exhibits A through E, respectively.

REPLY: Celgene admits that true and correct copies of the '262, '939, '428, and '427 patents are attached to the Complaint as Exhibits A-D, respectively, and, except as so admitted, denies the allegations of paragraph 28.

29. On or about June 12, 2012, the U.S. Patent & Trademark Office ("PTO") issued the '262 patent.

REPLY: Celgene admits the allegations of paragraph 29.

30. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the '262 patent and has the right to enforce the '262 patent.

REPLY: Celgene admits that Celgene is the owner of the '262 patent and has the right to enforce the '262 patent, and except as so admitted, denies the allegations of paragraph 30.

31. On or about March 18, 2014, the PTO issued the '939 patent.

REPLY: Celgene admits the allegations of paragraph 31.

32. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the '939 patent and has the right to enforce the '939 patent.

REPLY: Celgene admits that Celgene is the owner of the '939 patent and has the right to enforce the '939 patent, and except as so admitted, denies the allegations of paragraph 32.

33. On or about May 27, 2014, the PTO issued the ‘428 patent.

REPLY: Celgene admits the allegations of paragraph 33.

34. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the ’428 patent and has the right to enforce the ‘428 patent.

REPLY: Celgene admits that Celgene is the owner of the ’428 patent and has the right to enforce the ’428 patent, and except as so admitted, denies the allegations of paragraph 34.

35. On or about September 9, 2014, the PTO issued the ‘427 patent.

REPLY: Celgene admits the allegations of paragraph 35.

36. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the ‘427 patent and has the right to enforce the ‘427 patent.

REPLY: Celgene admits that Celgene is the owner of the ’427 patent and has the right to enforce the ’427 patent, and except as so admitted, denies the allegations of paragraph 36.

37. On or about November 13, 2001, the PTO issued the ‘720 patent.

REPLY: Celgene admits the allegations of paragraph 37.

38. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the ‘720 patent and has the right to enforce the ‘720 patent.

REPLY: Celgene admits that Celgene is the owner of the ’720 patent and has the right to enforce the ’720 patent, and except as so admitted, denies the allegations of paragraph 38.

39. On or about May 13, 2003, the PTO issued the ‘977 patent.

REPLY: Celgene admits the allegations of paragraph 39.

40. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the ‘977 patent and has the right to enforce the ‘977 patent.

REPLY: Celgene admits that Celgene is the owner of the ’977 patent and has the right to enforce the ’977 patent, and except as so admitted, denies the allegations of paragraph 40.

41. On or about June 29, 2004, the PTO issued the ‘784 patent.

REPLY: Celgene admits the allegations of paragraph 41.

42. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the '784 patent and has the right to enforce the '784 patent.

REPLY: Celgene admits that Celgene is the owner of the '784 patent and has the right to enforce the '784 patent, and except as so admitted, denies the allegations of paragraph 42.

43. On or about November 20, 2012, the PTO issued the '886 patent.

REPLY: Celgene admits the allegations of paragraph 43.

44. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the '886 patent and has the right to enforce the '886 patent.

REPLY: Celgene admits that Celgene is the owner of the '886 patent and has the right to enforce the '886 patent, and except as so admitted, denies the allegations of paragraph 44.

45. On or about January 7, 2014, the PTO issued the '531 patent.

REPLY: Celgene admits the allegations of paragraph 45.

46. On information and belief, Plaintiff/Counterclaim-Defendant is the owner of the '531 patent and has the right to enforce the '531 patent.

REPLY: Celgene admits that Celgene is the owner of the '531 patent and has the right to enforce the '531 patent, and except as so admitted, denies the allegations of paragraph 46.

47. Plaintiff/Counterclaim-Defendant purports to be the holder of approved New Drug Application ("NDA") No. 204026 for pomalidomide capsules, which is sold in the United States under the trademark POMALYST®.

REPLY: Celgene admits that it is the holder of NDA No. 204026 for pomalidomide capsules, 1 mg, 2 mg, 3 mg, and 4 mg, sold in the United States under the trademark POMALYST®, and except as so admitted, denies the allegations of paragraph 47.

48. Plaintiff/Counterclaim-Defendant listed the Patents-in-Suit in the FDA's Orange Book for POMALYST®, and continues to maintain such listings. As a consequence of listing the Patents-in-Suit in the Orange Book, Plaintiff is representing to the world that the Patents-in- Suit cover POMALYST® and pomalidomide, and that Patents-in-Suit could reasonably be asserted against anyone who files an ANDA referencing POMALYST®, including such ANDAs containing a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (also called a "Paragraph IV Certification") to one or more of the Patents-in-Suit.

REPLY: Paragraph 48 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits that it requested that the FDA list the '720, '977, '784, '262, '886, '531, '939, '428, and '427 patents in the Orange Book in connection with NDA No. 204026, and, except as so admitted, denies the allegations of paragraph 48.

49. Hetero filed ANDA No. 210236 with FDA seeking approval for Hetero's proposed pomalidomide capsules products described therein ("Hetero ANDA Products"), identifying NDA No. 204026 as the reference listed drug.

REPLY: Paragraph 49 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits on information and belief that Hetero alleges that it has filed ANDA No. 210236 with the FDA seeking approval for Hetero's proposed pomalidomide capsules products described therein ("Hetero ANDA Products"), identifying NDA No. 204026 as the reference listed drug, and, except as so admitted, denies the allegations of paragraph 49.

50. Hetero's ANDA seeks FDA approval to market the Hetero ANDA Products described within ANDA No. 210236 before the expiration of the Patents-in-Suit listed in the Orange Book, and Hetero's ANDA includes and maintains a Paragraph IV Certification as to each of the Patents-in-Suit. By letter dated March 29, 2017, Hetero notified Plaintiff/Counterclaim-Defendant of Hetero's Paragraph IV Certification as to each of the Patents-in-Suit, detailing the legal and factual bases as to why the Patents-in-Suit are invalid and/or not infringed by the products described in Hetero's ANDA No. 210236 ("the Notice Letter").

REPLY: Paragraph 50 states a legal conclusion for which no reply is required, and Celgene lacks information or knowledge sufficient to form a belief as to the truth of the allegations in paragraph 50. To the extent that a reply is required, Celgene admits on information and belief that Hetero's ANDA includes Paragraph IV certifications for the patents-in-suit, and except as so admitted, Celgene denies the allegations of paragraph 50.

51. In response to the Notice Letter, Plaintiff/Counterclaim-Defendant sued Hetero in this District for alleged infringement of the '262 patent, the '939 patent, the '428 patent, and the '427 patent, but not the '720 patent, the '977 patent, the '784 patent, the '886 patent, and the '531 patent. Celgene's suit triggered a statutory stay of FDA approval of Hetero's ANDA No. 210236.

REPLY: Paragraph 51 states a legal conclusion for which no reply is required. To the extent that a reply is required, Celgene admits that it sued Hetero in this Judicial District for the infringement of the '262 patent, the '939 patent, the '428 patent, and the '427 patent, refers to the Complaint with respect to its contents, that Hetero's ANDA No. 210236 is subject to a stay of FDA approval, and except as so admitted, denies the allegations of paragraph 51.

52. Despite the Notice Letter, Plaintiff/Counterclaim-Defendant maintains the listing of the Patents-in-Suit in the Orange Book for POMALYST®, thereby continuing to cause injury to Hetero.

REPLY: Celgene denies the allegations of paragraph 52.

Count I
(Declaratory Judgment of Alleged Invalidity of the '262 Patent)

53. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-52 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

54. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '262 patent.

REPLY: Paragraph 54 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing

case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '262 patent, and except as so admitted, denies the allegations of paragraph 54.

55. The claims of the '262 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 55.

56. The claims of the '262 patent are obvious under 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '262 patent was disclosed in the prior art before the earliest possible priority date of the '262 patent, including, but not limited to, those references disclosed in the Notice Letter. A person of ordinary skill in the art would have been motivated to combine those references as of the earliest possible priority date of the '262 patent, and would have had a reasonable expectation of success in doing so. As to the '262 patent, invalidating prior art references include at least: (a) S. Lentzsch et al., *S-3-Amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell nopasias in mice, 62 Cancer Research 2300 (April 15, 2002) ("the Lentzsch reference"); (b) Hideshima, et al., Thalidomide and its Analogs Overcome Resistance of Human Multiple Myeloma Cells to Conventional Therapy, 96 Blood 2943 (Nov. 1, 2000) ("the Hideshima reference"); (c) R.J. D'Amato, et al., Mechanism of Action of Thalidomide and 3-Aminothalidomide in Multiple Myeloma, 28 Seminars in Oncology 597 (Dec. 2001) ("the D'Amato reference"); (d) U.S. Patent No. 6,316,471 entitled "Isoindolines, Method of Use, and Pharmaceutical Compositions" issued on November 13, 2001 ("the '471 patent"); and (e) U.S. Patent No. 5,635,517, entitled "Method of Reducing TNFα Levels with Amino Substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo- and 1,3-dioxoisoindolines" issued on June 3, 1997 ("the '517 patent").*

REPLY: Celgene denies the allegations of paragraph 56.

57. There is no objective evidence of non-obviousness of the claims of the '262 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '262 patent.

REPLY: Celgene denies the allegations of paragraph 57.

58. The claims of the '262 patent are also invalid under 35 U.S.C. § 112, for lack of enablement. The '262 patent fails to describe, identify, or teach effective methods of treating multiple myeloma through administration of pomalidomide. The '262 patent does not provide any data, clinical or otherwise, regarding actual administration of pomalidomide to patients. As such, the claims of the '262 patent are invalid because the patent does not enable the full scope of the claims.

REPLY: Celgene denies the allegations of paragraph 58.

59. The claims of the '262 patent are also invalid under 35 U.S.C. § 112 for insufficient written description at least because the specification of the '262 patent does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '262 patent would not convey to a person of skill in the art that the inventor was in possession of the claimed subject matter because the '262 patent is devoid of any data, studies, or other evidence that the inventors had actually invented a method for treating multiple myeloma by administration of pomalidomide. As such, the claims of the '262 patent are invalid for lack of written description.

REPLY: Celgene denies the allegations of paragraph 59.

60. Hetero is entitled to a judicial declaration that the claims of the '262 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 60.

Count II
(Declaratory Judgment of Alleged Non-Infringement of the '262 Patent)

61. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-60 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

62. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '262 patent.

REPLY: Paragraph 62 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '262 patent, and except as so admitted, denies the allegations of paragraph 62.

63. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '262 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '262 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 63.

64. Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '262 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 64.

Count III
(Declaratory Judgment of Alleged Invalidity of the '939 Patent)

65. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-64 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

66. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '939 patent.

REPLY: Paragraph 66 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '939 patent, and except as so admitted, denies the allegations of paragraph 66.

67. The claims of the '939 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 67.

68. The claims of the '939 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '939 patent was disclosed in the prior art before the earliest possible priority date of the '939 patent, including, but not limited to, those references disclosed in the Notice Letter. A person of ordinary skill in the art would have been motivated to combine those references as of the earliest possible priority date of the '939 patent, and would have had a reasonable expectation of success in doing so. As to the '939 patent, invalidating prior art references include at least: (a) the Lentzsch reference, (b) the Hideshima reference, (c) the D'Amato reference, (d) the '471 patent, and (3) the '517 patent.

REPLY: Celgene denies the allegations of paragraph 68.

69. There is no objective evidence of non-obviousness of the claims of the '939 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '939 patent.

REPLY: Celgene denies the allegations of paragraph 69.

70. The claims of the '939 patent are also invalid under 35 U.S.C. § 112, for lack of enablement. The '939 patent fails to describe, identify, or teach effective methods of treating multiple myeloma through administration of pomalidomide. The '939 patent does not provide any data, clinical or otherwise, regarding actual administration of pomalidomide to patients. As such, the claims of the '939 patent are invalid because the patent does not enable the full scope of the claims.

REPLY: Celgene denies the allegations of paragraph 70.

71. The claims of the '939 patent are also invalid under 35 U.S.C. § 112 for insufficient written description at least because the specification of the '939 patent does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '939 patent would not convey to a person of skill in the art that the inventor was in possession of the claimed subject matter because the '939 patent is devoid of any data, studies, or other evidence that the inventors had actually invented a method for treating multiple myeloma by administration of pomalidomide. As such, the claims of the '939 patent are invalid for lack of written description.

REPLY: Celgene denies the allegations of paragraph 71.

72. Hetero is entitled to a judicial declaration that the claims of the '939 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 72.

Count IV
(Declaratory Judgment of Alleged Non-Infringement of the '939 Patent)

73. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-72 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

74. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '939 patent.

REPLY: Paragraph 74 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '939 patent, and except as so admitted, denies the allegations of paragraph 74.

75. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '939 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '939 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 75.

76. Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '939 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 76.

Count V
(Declaratory Judgment of Alleged Invalidity of the '428 Patent)

77. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-76 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

78. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '428 patent.

REPLY: Paragraph 78 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '428 patent, and except as so admitted, denies the allegations of paragraph 78.

79. The claims of the '428 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 79.

80. The claims of the '428 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '428 patent was disclosed in the prior art before the earliest possible priority date of the '428 patent, including, but not limited to, those references disclosed in the Notice Letter. A person of ordinary skill in the art would have been motivated to combine those references as of the earliest possible priority date of the '428 patent, and would have had a reasonable expectation of success in doing so. As to the '428 patent, invalidating prior art references include at least: (a) the Lentzsch reference, (b) the Hideshima reference, (c) the D'Amato reference, (d) the '471 patent, and (3) the '517 patent.

REPLY: Celgene denies the allegations of paragraph 80.

81. There is no objective evidence of non-obviousness of the claims of the '428 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '428 patent.

REPLY: Celgene denies the allegations of paragraph 81.

82. The claims of the '428 patent are also invalid under 35 U.S.C. § 112, for lack of enablement. The '428 patent fails to describe, identify, or teach effective methods of treating multiple myeloma through administration of pomalidomide. The '428 patent does not provide any data, clinical or otherwise, regarding actual administration of pomalidomide to patients. As such, the claims of the '428 patent are invalid because the patent does not enable the full scope of the claims.

REPLY: Celgene denies the allegations of paragraph 82.

83. The claims of the '428 patent are also invalid under 35 U.S.C. § 112 for insufficient written description at least because the specification of the '428 patent does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '428 patent would not convey to a person of skill in the art that the inventor was in possession of the claimed subject matter because the '428 patent is devoid of any data, studies, or other evidence that the inventors had actually invented a method for treating multiple myeloma by administration of pomalidomide. As such, the claims of the '428 patent are invalid for lack of written description.

REPLY: Celgene denies the allegations of paragraph 83.

84. Hetero is entitled to a judicial declaration that the claims of the '428 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 84.

Count VI
(Declaratory Judgment of Alleged Non-Infringement of the '428 Patent)

85. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-84 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

86. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '428 patent.

REPLY: Paragraph 86 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '428 patent, and except as so admitted, denies the allegations of paragraph 86.

87. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '428 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '428 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 87.

88. Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '428 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 88.

Count VII
(Declaratory Judgment of Alleged Invalidity of the '427 Patent)

89. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-88 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

90. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '427 patent.

REPLY: Paragraph 90 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '427 patent, and except as so admitted, denies the allegations of paragraph 90.

91. The claims of the '427 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 91.

92. The claims of the '427 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '427 patent was disclosed in the prior art before the earliest possible priority date of the '427 patent, including, but not limited to, the reference disclosed in the Notice Letter, U.S. Patent Publication No. 20070155791 A1 to Zeldis, which discloses administration of pomalidomide in an amount of 0.5 mg to 5 mg, including through the use of capsules with common pharmaceutically acceptable excipients.

REPLY: Celgene denies the allegations of paragraph 92.

93. There is no objective evidence of non-obviousness of the claims of the '427 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '427 patent.

REPLY: Celgene denies the allegations of paragraph 93.

94. Hetero is entitled to a judicial declaration that the claims of the '427 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 94.

Count VIII
(Declaratory Judgment of Alleged Non-Infringement of the '427 Patent)

95. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-94 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

96. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '427 patent.

REPLY: Paragraph 96 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '427 patent, and except as so admitted, denies the allegations of paragraph 96.

97. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '427 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '427 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 97.

98. Hetero also does not infringe the '427 patent because the patent claims do not cover Hetero's ANDA Product. The claims of the '427 patent all recite exact compositions comprising pomalidomide, which are not found in Hetero's ANDA, as detailed in the Notice Letter to Celgene. By way of a non-limiting example, Hetero's ANDA Product does not comprise pregelatinized starch, sodium stearyl fumarate, or spray dried mannitol in a total capsule weight in the amounts recited in the claims of the '427 patent, either literally or equivalently. For a second, non-limiting example, Hetero's ANDA Product does not comprise "5 mg of 100% pure pomalidomide," as recited in claims 11 and 12 of the '427 patent, either literally or equivalently.

REPLY: Celgene denies the allegations of paragraph 98.

99. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '427 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 99.

Count IX
(Declaratory Judgment of Alleged Invalidity of the '720 Patent)

100. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-99 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

101. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '720 patent.

REPLY: Paragraph 101 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '720 patent, and except as so admitted, denies the allegations of paragraph 101.

102. The claims of the '720 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 102.

103. The claims of the '720 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '720 patent was disclosed in the prior art before the earliest possible priority date of the '720 patent, including, but not limited to, the references disclosed in the Notice Letter: (a) the Thalomid® Capsules Revised Package Insert published on or around July 15, 1998; (b) U.S. Patent 5,832,449; (c) D.P. Keravich, *Challenges of Thalidomide Distribution in a Hospital Setting,* 56 Am. J. Health-Syst. Pharm. 1721; (d) J.B. Zeldis, *S.T.E.P.S.™ A Comprehensive Program for Controlling and Monitoring Access to Thalidomide,* 21 Clinical Therapeutics 319; (e) J.C. Mundt, *Interactive Voice Response Systems in Clinical Research and Treatmen,* 48 Psychiatric Services 611; (f) R.J. Powell, et al., *Guideline For the Clinical Use and Dispensing of Thalidomide,* 70 Postgrad. Med. J. 901; (g) A.A. Mitchell, et al., *A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin,* 333 New. Eng. J. Med. 101; and (h) B.R. Dishman, et al., *Pharmacists' Role in Clozapine Therapy at a Veterans Affairs Medical Center,* 51 Am. J. Hosp. Pharm. 899 (collectively, "the REMS References").

REPLY: Celgene denies the allegations of paragraph 103.

104. There is no objective evidence of non-obviousness of the claims of the '720 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '720 patent.

REPLY: Celgene denies the allegations of paragraph 104.

105. The '720 patent was the subject of *Inter Partes* Review Nos. IPR2015-01096, IPR2015-01102, and IPR2015-01103, each entitled *Coalition for Affordable Drugs VI LLC v. Celgene Corporation.* On October 26, 2016, the U.S. Patent & Trademark Office issued a final written decision in all three proceedings, holding in each that all claims of the '720 patent are unpatentable. The claims of the '720 patent are thus invalid for the reasons stated in the October 26, 2016 Final Written Decisions in *Inter Partes* Review Nos. IPR2015-01096, IPR2015-01102, and IPR2015-01103.

REPLY: Celgene admits that the '720 patent was the subject of *Inter Partes* Review Nos. IPR2015-01096, IPR2015-01102, and IPR2015-01103, that the rulings from those matters are currently the subject of pending rehearing requests, and that the '720 patent remains valid and enforceable during such time and during any subsequent appeal. Except as so admitted, Celgene denies the allegations of paragraph 105.

106. Hetero is entitled to a judicial declaration that the claims of the '720 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 106.

Count X
(Declaratory Judgment of Alleged Non-Infringement of the '720 Patent)

107. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-106 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

108. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '720 patent.

REPLY: Paragraph 108 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '720 patent, and except as so admitted, denies the allegations of paragraph 108.

109. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '720 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '720 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 109.

110. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '720 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 110.

Count XI
(Declaratory Judgment of Alleged Invalidity of the '977 Patent)

111. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-110 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

112. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '977 patent.

REPLY: Paragraph 112 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '977 patent, and except as so admitted, denies the allegations of paragraph 112.

113. The claims of the '977 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 113.

114. The claims of the '977 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '977 patent was disclosed in the prior art before the earliest possible priority date of the '977 patent, including, but not limited to, the REMS References disclosed in the Notice Letter.

REPLY: Celgene denies the allegations of paragraph 114.

115. There is no objective evidence of non-obviousness of the claims of the '977 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '977 patent.

REPLY: Celgene denies the allegations of paragraph 115.

116. Hetero is entitled to a judicial declaration that the claims of the '977 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 116.

Count XII
(Declaratory Judgment of Alleged Non-Infringement of the '977 Patent)

117. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-116 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

118. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '977 patent.

REPLY: Paragraph 118 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '977 patent, and except as so admitted, denies the allegations of paragraph 118.

119. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '977 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '977 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 119.

120. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '977 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 120.

Count XIII
(Declaratory Judgment of Alleged Invalidity of the '784 Patent)

121. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-120 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

122. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '784 patent.

REPLY: Paragraph 122 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '784 patent, and except as so admitted, denies the allegations of paragraph 122.

123. The claims of the '784 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 123.

124. The claims of the '784 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '784 patent was disclosed in the prior art before the earliest possible priority date of the '784 patent, including, but not limited to, the REMS References disclosed in the Notice Letter.

REPLY: Celgene denies the allegations of paragraph 124.

125. There is no objective evidence of non-obviousness of the claims of the '784 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '784 patent.

REPLY: Celgene denies the allegations of paragraph 125.

126. Hetero is entitled to a judicial declaration that the claims of the '784 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 126.

Count XIV
(Declaratory Judgment of Alleged Non-Infringement of the '784 Patent)

127. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-126 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

128. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '784 patent.

REPLY: Paragraph 128 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '784 patent, and except as so admitted, denies the allegations of paragraph 128.

129. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '784 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '784 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 129.

130. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '784 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 130.

Count XV
(Declaratory Judgment of Alleged Invalidity of the '886 Patent)

131. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-130 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

132. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '886 patent.

REPLY: Paragraph 132 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing

case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '886 patent, and except as so admitted, denies the allegations of paragraph 132.

133. The claims of the '886 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 133.

134. The claims of the '886 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '886 patent was disclosed in the prior art before the earliest possible priority date of the '886 patent, including, but not limited to, the REMS references disclosed in the Notice Letter.

REPLY: Celgene denies the allegations of paragraph 134.

135. There is no objective evidence of non-obviousness of the claims of the '886 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '886 patent.

REPLY: Celgene denies the allegations of paragraph 135.

136. Hetero is entitled to a judicial declaration that the claims of the '886 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 136.

Count XVI
(Declaratory Judgment of Alleged Non-Infringement of the '886 Patent)

137. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-136 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

138. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '886 patent.

REPLY: Paragraph 138 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '886 patent, and except as so admitted, denies the allegations of paragraph 138.

139. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '886 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '886 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 139.

140. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '886 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 140.

Count XVII
(Declaratory Judgment of Alleged Invalidity of the '531 Patent)

141. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-140 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

142. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* the invalidity of the '531 patent.

REPLY: Paragraph 142 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '531 patent, and except as so admitted, denies the allegations of paragraph 142.

143. The claims of the '531 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, or under judicially-created bases for invalidation, including but not limited, to 35 U.S.C. §§ 101, 102, 103, and/or 112.

REPLY: Celgene denies the allegations of paragraph 143.

144. The claims of the '531 patent are obvious 35 U.S.C. § 103 to a person of ordinary skill in the art because each and every element of each and every claim of the '531 patent was disclosed in the prior art before the earliest possible priority date of the '531 patent, including, but not limited to, the REMS References disclosed in the Notice Letter.

REPLY: Celgene denies the allegations of paragraph 144.

145. There is no objective evidence of non-obviousness of the claims of the '531 patent, nor would any such evidence, should it exist, have any nexus to the claimed purported inventions of the '531 patent.

REPLY: Celgene denies the allegations of paragraph 145.

146. Hetero is entitled to a judicial declaration that the claims of the '531 patent are invalid.

REPLY: Celgene denies the allegations of paragraph 146.

Count XVIII
(Declaratory Judgment of Alleged Non-Infringement of the '531 Patent)

147. Hetero re-alleges and incorporates by reference the allegations of paragraphs 1-146 as though fully set forth herein.

REPLY: Celgene incorporates its reply to the preceding paragraphs.

148. There is an actual, substantial, and continuing case or controversy between Hetero and the Plaintiff/Counterclaim-Defendant regarding, *inter alia,* non-infringement of the claims of the '531 patent.

REPLY: Paragraph 148 states legal conclusions for which no reply is required. To the extent that a reply is required, Celgene admits that there is an actual, substantial, and continuing case or controversy between Hetero and Celgene regarding, *inter alia*, the invalidity of the '531 patent, and except as so admitted, denies the allegations of paragraph 148.

149. The manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not —if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, the claims of the '531 patent, either literally or under the doctrine of equivalents. In particular, the claims of the '531 patent that cover pomalidomide or its use are invalid, and "invalidity operates as a complete defense to infringement for any product, forever." *Weatherchem Corp. v. J.L. Clark, Inc.,* 163 F.3d 1326, 1335 (Fed. Cir. 1998) *citing Blonder–Tongue Laboratories, Inc. v. University of Illinois Foundation,* 402 U.S. 313, 91 S.Ct. 1434, 28 L.Ed.2d 788 (1971).

REPLY: Celgene denies the allegations of paragraph 149.

150. As such, Hetero is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, importation, and/or marketing of Hetero's ANDA Product described in Hetero's ANDA has not infringed, does not infringe, and would not—if made, used, sold, offered for sale, imported or marketed—infringe, either directly or indirectly, any valid or enforceable claim of the '531 patent, either literally or under the doctrine of equivalents.

REPLY: Celgene denies the allegations of paragraph 150.

PRAYER FOR RELIEF

Celgene denies that Hetero is entitled to any relief on its Counterclaims, either as prayed for in its pleading or otherwise.

CELGENE'S AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in this Reply and to the ability to amend this Reply to seek and allege any and all defenses not presently known or that are revealed during the course of discovery or otherwise, Celgene asserts the following affirmative defenses in response to Hetero's Counterclaims:

First Defense: Failure to State a Claim

151. The Counterclaims fail to state any claim for which relief may be granted.

CELGENE'S COUNTER-COUNTERCLAIMS

Plaintiff Celgene Corporation ("Celgene"), by its undersigned attorneys, for its counter-counterclaims against Hetero Labs Limited, Hetero Labs Limited Unit-V, Hetero Drugs Limited, and Hetero USA, Inc.'s (together, "Hetero"), alleges as follows:

1. Plaintiff Celgene is a biopharmaceutical company committed to improving the lives of patients worldwide. Celgene focuses on, and invests heavily in, the discovery and development of products for the treatment of severe and life-threatening conditions. Celgene is a world leader in the treatment of many such diseases, including cancer. Celgene is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

2. On information and belief, Hetero Labs Limited ("Hetero Labs") is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad – 500 018, Andhra Pradesh, India.

3. On information and belief, Hetero Labs Limited Unit-V ("Hetero Unit-V") is a division of Hetero Labs Limited and is located at Polepally, Jadcherla, Mahabubnagar – 509 301, Andhra Pradesh, India.

4. On information and belief, Hetero Drugs Limited ("Hetero Drugs") is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad - 500018, Telangana, India.

5. On information and belief, Hetero USA, Inc. ("Hetero USA") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854.

6. On information and belief, Hetero USA acted as a regulatory agent of Hetero Unit-V with respect to ANDA No. 210236.

7. On information and belief, Hetero Labs Limited is a parent corporation of Hetero USA.

8. On information and belief, Hetero Unit-V is a division of Hetero Labs.

Nature of the Action

9. These Counter-counterclaims arise under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq*., arising from Hetero's filing of its Abbreviated New Drug Application ("ANDA") No. 210236 ("Hetero's ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of Celgene's POMALYST® drug products prior to the expiration of the United States Patent Nos. 6,315,720 ("'720 patent"), 6,561,977 ("'977 patent"), 6,755,784 ("'784 patent"), 8,315,886 ("'886 patent"), and 8,626,531 ("'531 patent") (collectively, the "REMS-patents-in-suit").

10. Hetero seeks a declaratory judgment of non-infringement and invalidity of the REMS-patents-in-suit.

The REMS-Patents-in-Suit

11. On November 13, 2001, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '720 patent, entitled "Methods for delivering a drug to a patient while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '720 patent is attached hereto as Exhibit A.

12. On May 13, 2003, the USPTO duly and lawfully issued the '977 patent, entitled "Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '977 patent is attached hereto as Exhibit B.

13. On June 29, 2004, the USPTO duly and lawfully issued the '784 patent, entitled "Methods for delivering a drug to a patient while restricting access to the drug by patients for

whom the drug may be contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '784 patent is attached hereto as Exhibit C.

14. On November 20, 2012, the USPTO duly and lawfully issued the '886 patent, entitled "Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '886 patent is attached hereto as Exhibit D.

15. On January 7, 2014, the USPTO duly and lawfully issued the '531 patent, entitled "Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated," to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the '531 patent is attached hereto as Exhibit E.

The POMALYST® Drug Product

16. Celgene holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for pomalidomide capsules (NDA No. 204026), which it sells under the trade name POMALYST®. POMALYST® is an FDA-approved medication used for the treatment of multiple myeloma.

17. The claims of the REMS-patents-in-suit cover, *inter alia*, systems and methods of use and administration of pomalidomide or pharmaceutical compositions containing pomalidomide.

18. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the REMS-patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to POMALYST®.

Jurisdiction and Venue

19. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

20. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Personal Jurisdiction

21. This Court has personal jurisdiction over Hetero USA by virtue of, *inter alia,* its systematic and continuous contacts with the State of New Jersey. On information and belief, Hetero USA's principal place of business is in Piscataway, New Jersey. On information and belief, Hetero USA is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business Id. No. 0400362826. On information and belief, Hetero USA is registered with the State of New Jersey's Department of Health as a drug wholesaler under Registration No. 5004050. On information and belief, Hetero USA purposefully has conducted and continues to conduct business in this Judicial District. By virtue of its physical presence in New Jersey, this Court has personal jurisdiction over Hetero USA.

22. On information and belief, Hetero USA is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in Hetero's ANDA. On information and belief, Hetero USA also prepares and/or aids in the preparation and submission of ANDAs to the FDA.

23. This Court has personal jurisdiction over Hetero Labs, Hetero Drugs, and Hetero Unit-V because, *inter alia*, they have: (1) purposely availed themselves of the privilege of doing

business in New Jersey, including directly or indirectly through their subsidiary, agent, and/or alter ego, Hetero USA, a company with its principal place of business in New Jersey; and (2) maintain extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero USA.

24. This Court has personal jurisdiction over Hetero because, *inter alia,* it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to Celgene in the State of New Jersey. On information and belief, Hetero intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Celgene in New Jersey and in this Judicial District.

25. On information and belief, Hetero USA, Hetero Labs, Hetero Unit-V, and Hetero Drugs work in concert either directly or indirectly through one or more of their wholly owned subsidiaries with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of generic pharmaceutical products throughout the United States, including in this Judicial District.

26. On information and belief, Hetero USA acts at the direction, and for the benefit, of Hetero Labs, Hetero Unit-V, and Hetero Drugs, and is controlled and/or dominated by Hetero Labs, Hetero Unit-V, and Hetero Drugs.

27. On information and belief, Hetero Drugs, Hetero Labs, Hetero Unit-V, and Hetero USA operate as a single integrated business. Hetero Drug's website notes that "Hetero's fully vertical integration of products and services ensures most cost-competitive supply of

pharmaceutical APIs and finished dosage products." http://heteroworld.com/pages/why-hetero/. On information and belief, Hetero Drugs and Hetero Labs share common corporate directors.

28. Hetero Drug's website states that "[w]ith a portfolio of more than 200 marketed products and 150 ANDAs filed across major therapeutic areas, the company is also the largest supplier of anti-retroviral drugs." https://heteroworld.com/pages/business-generics/.

29. On information and belief, Hetero USA, Hetero Labs, Hetero Unit-V, and Hetero Drugs have all previously been sued in this Judicial District and have not challenged personal jurisdiction. *See, e.g., Otsuka Pharm. Co., Ltd. v. Hetero Drugs Ltd., et al.,* Civil Action No. 15-161 (JBS)(KMW) (D.N.J.) (Hetero USA, Hetero Labs, Hetero Drugs); *AstraZeneca AB, et al. v. Hetero USA Inc., et al.,* Civil Action No. 16-2442 (MLC)(TJB) (D.N.J.) (Hetero USA and Hetero Labs); and *BTG Int'l Ltd., et al. v. Actavis Labs. FL, Inc., et al.,* Civil Action No. 15-5909 (KM)(JBC) (D.N.J.) (Hetero USA, Hetero Labs, Hetero Unit-V).

30. Hetero USA, Hetero Labs, Hetero Unit-V, and Hetero Drugs have further availed themselves of the jurisdiction of this Court by asserting counterclaims in this action.

Acts Giving Rise to These Counter-Counterclaims

31. Pursuant to Section 505 of the FFDCA, Hetero filed Hetero's ANDA seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of pomalidomide capsules, 1 mg, 2 mg, 3 mg, and 4 mg ("Hetero's Proposed Products"), before the REMS-patents-in-suit expire.

32. On information and belief, following FDA approval of Hetero's ANDA, Hetero Labs Limited, Hetero Labs Limited Unit-V, Hetero Drugs Limited, and Hetero USA, Inc. will work in concert with one another to make, use, sell, or offer to sell Hetero's Proposed Products throughout the United States, or import such generic products into the United States.

33. On information and belief, in connection with the filing of its ANDA as described above, Hetero provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Hetero's Paragraph IV Certification"), alleging that the claims of the REMS-patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Hetero's ANDA.

34. No earlier than March 30, 2017, Hetero sent written notice of its Paragraph IV Certification to Celgene ("Hetero's Notice Letter"). Hetero's Notice Letter alleged that the claims of the REMS-patents-in-suit are invalid and/or will not be infringed by the activities described in Hetero's ANDA. Hetero's Notice Letter also informed Celgene that Hetero seeks approval to market Hetero's Proposed Products before the REMS-patents-in-suit expire. Hetero specifically directed Hetero's Notice Letter to Celgene's headquarters in Summit, New Jersey, in this Judicial District.

Count I
(Infringement of the '720 Patent)

35. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Products, prior to the expiration of the '720 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

36. There is a justiciable controversy between Celgene and Hetero as to the infringement of the '720 patent.

37. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '720 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States.

38. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '720 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '720 patent and knowledge that its acts are encouraging infringement.

39. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '720 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Products are especially adapted for a use that infringes one or more claims of the '720 patent and that there is no substantial non-infringing use for Hetero's Proposed Products.

40. Celgene will be substantially and irreparably damaged and harmed if Hetero's infringement of the '720 patent is not enjoined.

41. Celgene does not have an adequate remedy at law.

42. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II
(Infringement of the '977 Patent)

43. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed

Products, prior to the expiration of the '977 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

44. There is a justiciable controversy between Celgene and Hetero as to the infringement of the '977 patent.

45. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '977 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States.

46. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '977 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '977 patent and knowledge that its acts are encouraging infringement.

47. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '977 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Products are especially adapted for a use that infringes one or more claims of the '977 patent and that there is no substantial non-infringing use for Hetero's Proposed Products.

48. Celgene will be substantially and irreparably damaged and harmed if Hetero's infringement of the '977 patent is not enjoined.

49. Celgene does not have an adequate remedy at law.

50. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III
(Infringement of the '784 Patent)

51. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Products, prior to the expiration of the '784 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

52. There is a justiciable controversy between Celgene and Hetero as to the infringement of the '784 patent.

53. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '784 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States.

54. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '784 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '784 patent and knowledge that its acts are encouraging infringement.

55. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '784 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, Hetero has had and continues to have knowledge that

Hetero's Proposed Products are especially adapted for a use that infringes one or more claims of the '784 patent and that there is no substantial non-infringing use for Hetero's Proposed Products.

56. Celgene will be substantially and irreparably damaged and harmed if Hetero's infringement of the '784 patent is not enjoined.

57. Celgene does not have an adequate remedy at law.

58. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV
(Infringement of the '886 Patent)

59. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Products, prior to the expiration of the '886 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

60. There is a justiciable controversy between Celgene and Hetero as to the infringement of the '886 patent.

61. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '886 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States.

62. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '886 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will

intentionally encourage acts of direct infringement with knowledge of the '886 patent and knowledge that its acts are encouraging infringement.

63. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '886 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Products are especially adapted for a use that infringes one or more claims of the '886 patent and that there is no substantial non-infringing use for Hetero's Proposed Products.

64. Celgene will be substantially and irreparably damaged and harmed if Hetero's infringement of the '886 patent is not enjoined.

65. Celgene does not have an adequate remedy at law.

66. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V
(Infringement of the '531 Patent)

67. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein. Hetero's submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Hetero's Proposed Products, prior to the expiration of the '531 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

68. There is a justiciable controversy between Celgene and Hetero as to the infringement of the '531 patent.

69. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '531 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States.

70. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '531 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '531 patent and knowledge that its acts are encouraging infringement.

71. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '531 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Hetero's Proposed Products in the United States. On information and belief, Hetero has had and continues to have knowledge that Hetero's Proposed Products are especially adapted for a use that infringes one or more claims of the '531 patent and that there is no substantial non-infringing use for Hetero's Proposed Products.

72. Celgene will be substantially and irreparably damaged and harmed if Hetero's infringement of the '531 patent is not enjoined.

73. Celgene does not have an adequate remedy at law.

74. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Celgene respectfully requests the following relief:

(A) A Judgment that Hetero has infringed the REMS-patents-in-suit by submitting ANDA No. 210236;

(B) A Judgment that Hetero has infringed, and that Hetero's making, using, selling, offering to sell, or importing Hetero's Proposed Products will infringe one or more claims of the REMS-patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 210236 be a date which is not earlier than the later of the expiration of the REMS-patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Hetero and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Hetero's Proposed Products until after the expiration of the REMS-patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Hetero, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any systems and methods of use and administration of pomalidomide or pharmaceutical compositions containing pomalidomide as claimed in the REMS-patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the REMS-patents-in-suit, until after the expiration of the REMS-patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Hetero's Proposed Products will directly infringe, induce and/or contribute to infringement of the REMS-patents-in-suit;

(G) To the extent that Hetero has committed any acts with respect to the systems and methods claimed in the REMS-patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Celgene damages for such acts;

(H) If Hetero engages in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Hetero's Proposed Products prior to the expiration of the REMS-patents-in-suit, a Judgment awarding damages to Celgene resulting from such infringement, together with interest;

(I) A Judgment declaring that the REMS-patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Celgene its attorneys' fees incurred in this action;

(K) A Judgment awarding Celgene its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: August 17, 2017

By: s/ Charles M. Lizza

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EXHIBIT A

US006315720B1

(12) **United States Patent**
Williams et al.

(10) **Patent No.: US 6,315,720 B1**
(45) **Date of Patent: Nov. 13, 2001**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE AVOIDING THE OCCURRENCE OF AN ADVERSE SIDE EFFECT KNOWN OR SUSPECTED OF BEING CAUSED BY THE DRUG**

(75) Inventors: **Bruce A. Williams**, Flemington; **Joseph K. Kaminski**, Hampton, both of NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/694,217**

(22) Filed: **Oct. 23, 2000**

(51) **Int. Cl.**[7] **A61B 5/00**
(52) **U.S. Cl.** **600/300**; 235/375
(58) **Field of Search** 600/300, 304, 600/551; 395/202–210; 128/630; 706/23, 2, 3; 235/375

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(57) **ABSTRACT**

Improved methods for delivering to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug are disclosed. The methods are of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber, pharmacy and patient have been properly registered in the medium before the patient is approved to receive the drug. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to the side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

32 Claims, No Drawings

METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE AVOIDING THE OCCURRENCE OF AN ADVERSE SIDE EFFECT KNOWN OR SUSPECTED OF BEING CAUSED BY THE DRUG

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for

example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or

the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is

contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional

pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be

generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the

patient is directed to return to the prescriber for detenriination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;

b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;

c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;

d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and

e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled.

2. The method of claim **1** wherein, in response to said risk group assignment, said patient is counseled as to the risks of taking said drug and advised as to risk avoidance measures.

3. The method of claim **2** wherein said counseling comprises full disclosure of said risks.

4. The method of claim **3** wherein said prescription is filled only following said full disclosure and informed consent of said patient.

5. The method of claim **4** wherein said risk group assignment and said informed consent is verified by said prescriber at the time that said patient is registered in said computer readable storage medium.

6. The method of claim **5** wherein said risk group assignment and said informed consent is transmitted to said computer readable storage medium by facsimile and interpreted by optical character recognition software.

7. The method of claim **1** wherein said set of information includes the results of diagnostic testing.

8. The method of claim **7** wherein said diagnostic testing is probative of the onset of said adverse side effect.

9. The method of claim **7** wherein said diagnostic testing is probative of the concentration of said drug in a tissue of said patient.

10. The method of claim **7** wherein said diagnostic testing comprises genetic testing.

11. The method of claim **1** wherein said side effect is likely to arise in said patient.

12. The method of claim **1** wherein said side effect is likely to arise in a foetus carried by said patient.

13. The method of claim **1** wherein said side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of said patient.

14. The method of claim **13** wherein said recipient is a sexual partner of said patient.

15. The method of claim **1** further comprising:

f. defining for each said risk group a second set of information to be collected from said patient on a periodic basis;

g. obtaining said second set of information from said patient; and

h. entering said second set of information in said medium before said patient is approved to receive said drug.

16. The method of claim **15** wherein said second set of information comprises a survey regarding said patient's behavior and compliance with said risk avoidance measures.

17. The method of claim **16** wherein said survey is conducted telephonically using an integrated voice response system.

18. The method of claim **16** wherein said patient is a female of childbearing potential and said second set of information comprises the results of a pregnancy test.

19. The method of claim **18** wherein said periodic interval comprises about 28 days.

20. The method of claim **1** further comprising providing said patient with a contraceptive device or formulation.

21. The method of claim **1** wherein said adverse side effect comprises a teratogenic effect.

22. The method of claim **1** wherein said drug is thalidomide.

23. The method of claim **21** wherein said teratogenic effect is likely to arise in a foetus carried by said patient.

24. The method of claim **21** wherein said teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of said patient.

25. The method of claim **24** wherein said recipient of the bodily fluid of said patient is a sexual partner of said patient.

26. The method of claim **21** wherein said set of information includes the results of a pregnancy test.

27. The method of claim **26** wherein said prescription is filled for no more than about 28 days.

28. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;

b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;

c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;

d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and

e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled,

wherein said adverse side effect is likely to arise in patients who take said drug in combination with at least one other drug.

29. The method of claim **28** wherein said set of information is also probative of the likelihood that said patient may take said drug and said other drug in combination.

30. The method of claim **28** wherein said set of information includes the results of diagnostic testing.

31. The method of claim **30** wherein said diagnostic testing comprises testing for evidence of the use of said other drug.

32. The method of claim **30** wherein said diagnostic testing comprises testing for evidence which is indicative of the onset of said adverse side effect.

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EXHIBIT B

US006561977B2

(12) **United States Patent**
Williams et al.

(10) **Patent No.: US 6,561,977 B2**
(45) **Date of Patent: *May 13, 2003**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(58) **Field of Search** 600/300–301, 600/304, 551; 395/202–210; 706/23, 2–3; 705/2–4; 735/375; 707/102

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

34 Claims, No Drawings

METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000 U.S. Pat. No. 6,315,720.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that

such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registra-

tion card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the

drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided

verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will

be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing.

Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescript2ion to a registered pharmacy, the computer readable storage medium is consulted to verify tha2t the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for

the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence

amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from a patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment in the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code to be retrieved by the pharmacy before the prescription is filled.

2. A method according to claim **1** further comprising registering in the medium the physician who prescribed the drug.

3. A method according to claim **1** further comprising registering the pharmacy in the medium.

4. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim **4** wherein the counseling comprises full disclosure of the risks.

6. The method of claim **5** wherein the prescription is filled only following the full disclosure and informed consent of the patient.

7. The method of claim **6** wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim **7** wherein the risk group assignment and the informed consent is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim **1** wherein the set of information includes the results of diagnostic testing.

10. The method of claim **9** wherein the diagnostic testing comprises genetic testing.

11. The method of claim **9** wherein the diagnostic testing is probative of the onset of the adverse side effect.

12. The method of claim **9** wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.

13. The method of claim **1** wherein the side effect is likely to arise in the patient.

14. The method of claim **1** wherein the side effect is likely to arise in a foetus carried by the patient.

15. The method of claim **1** wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.

16. The method of claim **15** wherein the recipient is a sexual partner of the patient.

17. The method of claim **1** further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

18. The method of claim **17** wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.

19. The method of claim **18** wherein the survey is conducted telephonically using an integrated voice response system.

20. The method of claim **17** wherein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.

21. The method of claim **18** wherein the periodic interval comprises about 28 days.

22. The method of claim **1** further comprising providing the patient with a contraceptive device or formulation.

23. The method of claim **1** wherein the adverse side effect comprises a teratogenic effect.

24. The method of claim **23** wherein the drug is thalidomide.

25. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by the patient.

26. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.

27. The method of claim **26** wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.

28. The method of claim **23** wherein the set of information includes the results of a pregnancy test.

29. The method of claim **28** wherein the prescription is filled for no more than about 28 days.

30. The method of claim **1** wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.

31. The method of claim **30** wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.

32. The method of claim **30** wherein the set of information includes the results of diagnostic testing.

33. The method of claim **32** wherein the diagnostic testing comprises testing for evidence of the use of the other drug.

34. The method of claim **32** wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

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EXHIBIT C

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Williams et al.

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(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 34 days.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

34 Claims, No Drawings

METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of patent application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of patent application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community

anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to

receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups; and

d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a

registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise

female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the

patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug.

Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the sane, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has received an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;

b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;

c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;

d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and

e. upon a determination that the risk is acceptable, generating the prescription approval code to be received by the pharmacy before the prescription is filled.

2. A method according to claim **1** further comprising registering in the medium the physician who prescribed the drug.

3. A method according to claim **1** further comprising registering the pharmacy in the medium.

4. The method of claim **1** further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim **4** wherein the counseling comprises full disclosure of the risks.

6. The method of claim **5** wherein the prescription is filled only following the full disclosure and informed consent of the patient.

7. The method of claim **6** wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim **7** wherein the risk group assignment and the informed consent is transmitted to the com-

puter readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim **1** wherein the set of information comprises the results of diagnostic testing.

10. The method of claim **9** wherein the diagnostic testing comprises genetic testing.

11. The method of claim **9** wherein the diagnostic testing is probative of the onset of the adverse side effect.

12. The method of claim **9** wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.

13. The method of claim **1** wherein the side effect is likely to arise in the patient.

14. The method of claim **1** wherein the side effect is likely to arise in a foetus carried by the patient.

15. The method of claim **1** wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.

16. The method of claim **15** wherein the recipient is a sexual partner of the patient.

17. The method of claim **1** further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

18. The method of claim **17** wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.

19. The method of claim **18** wherein the survey is conducted telephonically using an integrated voice response system.

20. The method of claim **17** herein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.

21. The method of claim **18** wherein the periodic interval comprises about 28 days.

22. The method of claim **1** further comprising providing the patient with a contraceptive device or formulation.

23. The method of claim **1** wherein the adverse side effect comprises a teratogenic effect.

24. The method of claim **23** wherein the drug is thalidomide.

25. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by the patient.

26. The method of claim **23** wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.

27. The method of claim **26** wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.

28. The method of claim **26** wherein the set of information includes the results of a pregnancy test.

29. The method of claim **28** wherein the prescription is filled for more than about 28 days.

30. The method of claim **1** wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.

31. The method of claim **30** wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.

32. The method of claim **30** wherein the set of information includes the results of diagnostic testing.

33. The method of claim **32** wherein the diagnostic testing comprises testing for evidence of the use of the other drug.

34. The method of claim **32** wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

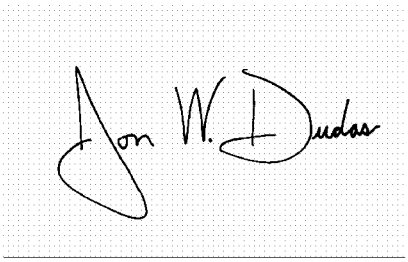
PATENT NO. : 6,755,784 B2
DATED : June 29, 2004
INVENTOR(S) : Bruce A. Williams and Joseph A. Kaminski

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20,
Line 20, cancel the text "filled for more than about 28 days." and insert -- filled for no more than about 28 days. --.

Signed and Sealed this

Third Day of May, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT D

US008315886B2

(12) **United States Patent**
Williams et al.

(10) **Patent No.: US 8,315,886 B2**
(45) **Date of Patent: *Nov. 20, 2012**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 155 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 11/437,551, filed on May 19, 2006, now Pat. No. 7,959,566, which is a continuation of application No. 11/028,144, filed on Jan. 3, 2005, now Pat. No. 7,141,018, which is a continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
G06Q 50/00 (2006.01)

(52) **U.S. Cl.** **705/2**

(58) **Field of Classification Search** 705/2
See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

7 Claims, No Drawings

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METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and

aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which

prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in

detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of

child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the

patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an addi-

tional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of childbearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing

the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate

that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share

similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A method of treating a male patient having a disease or condition responsive to a teratogenic drug comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription, wherein the generation of the prescription approval code comprises the following steps:

(a) via a computer readable storage medium, registering a prescriber and the pharmacy with a distributor of a teratogenic drug;

(b) determining whether the patient is able to understand and carry out instructions;

(c) upon determination that the patient is able to carry out the instructions, providing verbal and written warnings of the hazard of taking the drug and exposing fetus to the drug;

(d) further providing verbal and written warnings of the risk of possible contraception failure and of the need to use barrier contraception when having sexual intercourse with women of child bearing potential;

(e) obtaining acknowledgement of said warnings from the patient;

(f) via a computer readable storage medium, registering the patient with the distributor; and

(g) upon obtaining the acknowledgement and registrations, generating via a computer readable storage medium the prescription approval code to be retrieved by the pharmacy before the prescription is filled; and

(h) upon retrieving a prescription approval code, administering the drug to the patient.

2. The method of claim **1**, wherein the acknowledgement requires the patient's acknowledgement of one or more of the following:

(a) the understanding that the drug must not be taken if unprotected sex cannot be avoided;

(b) the understanding of potential birth defects;

(c) that the patient has been advised of the need for barrier contraception by the prescriber;

(d) the obligation to inform the prescriber if the patient's sexual partner is suspected of becoming or being pregnant;

(e) that the drug is solely for the use of the patient himself and must not be shared with any other person;

(f) that the patient has read the information brochure or viewed the information film on the drug;

(g) that the semen or blood must not be donated during the drug treatment;

(h) that all of the patient's inquiries regarding the drug treatment have been answered by the prescribing physician; or

(i) the patient's understanding that participation in a survey and patient registry is required during the drug treatment.

3. The method of claim **1** further comprising providing the patient, prior to generation of the approval code, with warnings of the side effects associated with administration of the drug, wherein said side effects are non-teratogenic side effects.

4. The method of claim **1** further comprising obtaining a written authorization by the prescriber prior to generation of the approval code.

5. The method of claim **1**, wherein the prescription approval code is retrieved from a computer readable storage medium.

6. The method of claim **1**, wherein the acknowledgement is a written informed consent.

7. The method of claim **6**, wherein the written informed consent is registered in the medium prior to generation of the prescription approval code.

* * * * *

EXHIBIT E

US008626531B2

(12) **United States Patent**
Williams et al.

(10) **Patent No.: US 8,626,531 B2**
(45) **Date of Patent: *Jan. 7, 2014**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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USPC **705/2**

(58) **Field of Classification Search**
USPC 705/2
See application file for complete search history.

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

40 Claims, No Drawings

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METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/966,261, filed Dec. 13, 2010, which is a continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, now U.S. Pat. No. 7,959,566, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public

Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while

avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
c. in response to the information set, assigning the patient to at least one of the risk groups; and
d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the

methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug,

such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the pre-

scriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to be being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree

to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of childbearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuburculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is

not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol.

Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A system for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the system comprising:

a computer device including:

a computer readable medium having stored therein the plurality of risk groups, the at least one risk group assignment, and registration information of the patient;

the computer device configured to provide:

an interface configured to receive an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

a generator configured to generate a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and based on comparison of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug, such that the risk group assignment is based on a predefined set of risk parameters for the contraindicated drug; and

an interface configured to send an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

2. The system of claim **1** further comprising the computer readable medium having stored thereon further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

3. The system of claim **2**, wherein the further information includes an informed consent of the patient for receiving the drug.

4. The system of claim **3**, wherein the further information is compared with the drug request before generation of the prescription approval code.

5. The system of claim **4**, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

6. The system of claim **4**, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

7. The system of claim 4, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

8. The system of claim 7, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

9. The system of claim 8, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

10. The system of claim 1 further comprising additional communication over the network via on-line communication.

11. The system of claim 10 further comprising the interface including an integrated voice response system such that the network is a telecommunications network.

12. The system of claim 1 computer readable medium having stored thereon risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

13. The system of claim 12 further comprising the on-line transmission to the pharmacist such that the generated prescription approval code is omitted from the on-line transmission to the pharmacist and a request for additional information is included in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

14. The system of claim 13, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

15. The system of claim 13 further configured such that the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

16. The system of claim 15, wherein the additional information is defined for updating parameters of the patient risk group assignment on a periodic basis.

17. The system of claim 16, wherein the providing of the additional information to the computer readable medium results in an update of the patient risk group assignment.

18. The system of claim 15 further comprising the interface configured for providing the generated approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

19. The system of claim 12, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

20. The system of claim 19, wherein additional information when received by the interface in reply to the request for additional information is stored in the computer readable medium.

21. A method for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the method comprising the steps of:

accessing, using a computer device, a computer readable medium having stored thereon the plurality of risk groups, the at least one risk group assignment, and registration information for the patient in computer readable medium;

receiving, using the computer device, an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

comparing, using the computer device, the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and comparing of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug,

generating, using the computer device, a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient if confirmed the registered patient is eligible to receive the drug; and

sending, sing the computer device, an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

22. The method of claim 21 further comprising the step of storing further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

23. The method of claim 22, wherein the further information includes an informed consent of the patient for receiving the drug.

24. The method of claim 23, wherein the further information is compared with the drug request before generation of the prescription approval code.

25. The method of claim 24, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

26. The method of claim 24, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

27. The method of claim 24, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

28. The method of claim **27**, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

29. The method of claim **28**, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

30. The method of claim **21** further comprising additional communication over the network via on-line communication.

31. The method of claim **30**, wherein the receiving of the on-line transmission of the pharmacist prescription is via an integrated voice response system such that the network is a telecommunications network.

32. The method of claim **21** further comprising the step of storing risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

33. The method of claim **32** further comprising the step of omitting the generated prescription approval code from the on-line transmission to the pharmacist and including a request for additional information in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

34. The method of claim **33**, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

35. The method of claim **33**, wherein the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

36. The method of claim **35** further comprising the step of using the additional information obtained from the patient for updating parameters of the patient risk group assignment on a periodic basis.

37. The method of claim **36** further comprising the step of using the additional information to update the patient risk group assignment.

38. The method of claim **35** further comprising the step of providing the generated prescription approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

39. The method of claim **32**, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

40. The method of claim **39** further comprising the step of storing the additional information in the computer readable medium when received in reply to the request for additional information.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,626,531 B2
APPLICATION NO. : 13/591622
DATED : January 7, 2014
INVENTOR(S) : Bruce A. Williams and Joseph K. Kaminski

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 19,
Claim 15, lines 49-50, delete "that the least" and insert -- that the at least --.

Column 20,
Claim 21, line 35, delete "sing the computer device," and insert -- using the computer device, --.

Column 22,
Claim 35, line 10, after "wherein the" insert -- at --.

Signed and Sealed this
First Day of April, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20,
Claim 20, line 1, delete "claim 19," and insert -- claim 13, --.

Column 22,
Claim 40, line 29, delete "claim 39" and insert -- claim 33 --.

Signed and Sealed this
Fourteenth Day of June, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office